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Research Article

Ketofol versus Dexmedetomidine for Prevention of Emergence Delirium in Pediatric Patients Undergoing Squint Surgeries: A Randomized Clinical Study

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ABSTRACT

Background: A common adverse event in pediatric patients after surgery is emergence delirium (ED), which manifests as agitation, disorientation, and changes in perception (such as hypersensitivity to stimuli) together with inconsolable crying and moaning. This study compared the efficacy of ketofol versus dexmedetomidine (DEX) in preventing ED in children undergoing squint surgeries.

Methods: This prospective, randomized, clinical double-blind study enrolled 52 children aged 2–6 years, of both sexes, undergoing squint surgery. Patients were divided into two equal groups. Five minutes after securing the airway, DEX was infused at 0.2 µg/kg/h in Group D, and Ketofol (1:4 ketamine to propofol) was infused at 80 µg/kg/min propofol and 20 µg/kg/min ketamine in Group K.

Results: The incidence of intraoperative bradycardia and hypotension was not substantially different between the two groups. There was no significant difference in heart rate, mean arterial blood pressure, or peripheral oxygen saturation between groups intraoperatively and postoperatively. PAED and FLACC scores were insignificantly different between the two groups. Postoperative rescue analgesia and rescue sedation showed insignificant differences between groups.

Conclusion: Ketofol and DEX are equally effective in preventing emergence delirium (ED) in children undergoing squint surgery while maintaining stable hemodynamics.

Introduction

Emergence delirium (ED) is a prevalent after-surgery adverse event in pediatrics, familiar with disorientation, confusion, and alterations in perception such as hypersensitivity to stimuli, inconsolable crying, and moaning [1-3].

There are many risk factors contributing to ED, including patient age, preoperative anxiety, inadequate adaptive behavior, separation from parents, anesthetic drug side effects, sudden arousal in an unfamiliar environment, and the type of surgical operation, including ophthalmological operations (strabismus surgeries) [3-4]. ED appeared to be accompanied by undesirable consequences, as the child may remove intravenous (IV) devices, urinary catheters, and surgical drains, which may cause injury to the surgical site. Children experiencing ED necessitate additional care and a longer stay in the post-anesthesia care unit (PACU) [1-2]. Accordingly, the prevention of such complications is

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mandatory [5-7]. Dexmedetomidine (DEX) is a selective α2-adrenergic receptor agonist that inhibits sympathetic activity in the central nervous system, thereby providing sedative, analgesic, and anxiolytic properties. In contrast, ketamine is a noncompetitive antagonist of the N-methyl-D-aspartic acid (NMDA) receptor; it has dose-dependent sedative, analgesic, and amnesic properties [8].

One of the anesthetics used for general anesthesia (GA) induction and maintenance is propofol, which has sedative and hypnotic effects with a quick start and short duration, allowing for quick recovery. Many studies demonstrated that propofol administration for the maintenance of anesthesia remarkably reduces ED incidence [9]. Despite many previous studies investigating effectiveness of adjunctive anesthetic agents in the prevention of ED, there is lack of studies that focused on the comparison between the efficacy of DEX and Ketofol in lowering the frequency of ED in preschool pediatric population undergoing eye surgeries, a prior research compared the effects of DEX and ketofol when administered as a single bolus dose 10 minutes before surgery's conclusion in children undergoing orthopedic procedures under sevoflurane-based general anesthesia, with the age range of the subjects being 3 to 6 years old [10], the one contrasted comparison of DEX with ketofol given as a single bolus dosage 10 minutes before to surgery end in patients undergoing oropharyngeal and urological procedures involving children aged 3 to 10 [11]. This research aimed to compare the effectiveness of Ketofol and DEX for the prevention of ED in pediatric patients undergoing squint surgery.

Methods

Ethical considerations

This study obtained approval from the Research Ethics Committee at Cairo University (MD-184-2023) and was registered on ClinicalTrials.gov (NCT06545890). Every member of the patients' families gave their signed, informed consent.

Study design, setting, duration, and eligibility criteria

This prospective, randomized, double-blinded clinical trial took place at Cairo University Hospitals in Egypt from November 2023 to April 2024. The study enrolled 52 children aged between 2 and 6 years old, of both sexes, belonging to the American Society of Anesthesiologists (ASA) I or II physical status, who underwent squint surgery. Exclusion criteria included a patient's history of a neurological condition that would impact the evaluation of ED postoperatively, as well as sensitivity to any of the research medications.

Randomization and blindness

A computer-generated randomization sequence was employed to assign participants to the study groups, with allocation concealment achieved by the use of sealed, opaque envelopes. In Group D, five minutes after the airway was secured, an infusion of dexmedetomidine (DEX; Medrelaxmidine-ARABCOMED) was initiated at a rate of 0.2 µg/kg/h. In Group K, five minutes following the induction of anesthesia, an infusion of a ketamine-propofol combination (Ketofol) was commenced. Ketofol was prepared by combining ketamine and propofol (Propofol-Lipuro 1%) in a ratio of 1:4, and it was administered at infusion rates of 4.8 mg/kg/h for propofol (corresponding to 80 µg/kg/min) and 1.2 mg/kg/h for ketamine (corresponding to 20 µg/kg/min). The ketamine-propofol solution was meticulously compounded by adding 40 mg of ketamine to 160 mg of propofol (Propofol-Lipuro 1%) and subsequently diluting the mixture to a total volume of 20 mL with 0.9% normal saline, yielding an infusion rate of 0.6 mL/kg/h.

The principal investigator, who also functioned as the attending anesthesiologist, was solely responsible for preparing the syringes containing the study medications. To maintain blinding, these syringes were enveloped in aluminum foil and sealed using the opaque envelope technique before being transferred to a secondary investigator immediately before administration to the pediatric patients. Overseeing the monitoring and data collection procedures simultaneously was a resident anesthesiologist who had been blinded to the names and allocations of the research medicines.

Intervention

Before the operative procedure, all patients satisfying the inclusion criteria underwent a rigorous evaluation to confirm adherence to fasting protocols. While clear oral liquids were permitted up to two hours before the scheduled surgery, a minimum fasting period of six hours was mandated for all patients. Patients were admitted to the preoperative preparation room one hour before the scheduled procedure, during which a comprehensive evaluation was conducted, including the documentation of age and body weight. The premedication was 0.2 mg/kg of midazolam and 0.02 mg/kg of atropine, which were injected intramuscularly.

In the operating room, standard monitoring procedures were instituted. These comprised continuous assessment of oxygen saturation (SpO_2), electrocardiography (ECG), and non-invasive blood pressure monitoring using the Dräger Infinity Vista XL system. Inhalational induction was achieved with sevoflurane at a concentration of 5%, and following the loss of consciousness, an intravenous cannula was inserted. After the patient's muscles were relaxed with atracurium at a dosage of 0.5 mg/kg, an endotracheal tube of the correct size was inserted. A second intravenous cannula was then established to facilitate the infusion of the study medications. The

anesthetic depth was adjusted to keep the heart rate (HR) and mean arterial pressure (MAP) within 20% of their baseline values. A mixture of 2% sevoflurane and 50% oxygen was used to maintain the anesthesia. Additional doses of atracurium (0.1 mg/kg) were administered every 30 minutes to ensure sustained neuromuscular blockade, and controlled ventilation was employed using the Dräger Infinity Vista XL anesthesia machine to maintain end-tidal carbon dioxide ($EtCO_2$) levels between 32 and 34 mmHg. Intraoperative hemodynamic parameters, specifically HR and MAP, were meticulously recorded at five-minute intervals. In the event of bradycardia or hypotension during the operation, the patient was given atropine intravenously at a dose of 0.02 mg/kg, and the minimum alveolar concentration (MAC) of sevoflurane was reduced to treat hypotension. Fluid management was carried out using Ringer's Lactate, with dosages adjusted according to each patient's body weight. Additionally, all patients received 15 mg/kg of paracetamol intravenously. The infusion of the research medications was stopped ten minutes before the expected end of the operation. Once the surgical procedure was over, the patient was taken off of sevoflurane, and neuromuscular blockade was reversed with a combination of 0.05 mg/kg of neostigmine and 0.02 mg/kg of atropine. When the patient showed signs of complete recovery, such as opening their eyes on their own, moving around with purpose, and maintaining an appropriate tidal volume, they were extubated. Thereafter, they were taken to the PACU, where they were given more oxygen through a face mask to keep their oxygen saturation levels over 95%. The Pediatric Anesthesia Emergence Delirium (PAED) scale was used to evaluate ED in the PACU at set intervals, including immediately after admission and 5, 10, 15, 20, 25, and 30 minutes later. An ED diagnosis was rendered if the PAED score reached or exceeded 10, prompting the administration of rescue sedation with propofol at a dose of 1 mg/kg. Concurrently, postoperative pain was evaluated using the Face, Legs, Activity, Cry, and Consolability (FLACC) scale immediately after the transfer to the PACU. The pain scores were calculated as follows: 0 meant no pain at all, 1–3 meant a little pain, 4–6 meant moderate pain, and 7–10 meant extreme pain. A dose of 1 μg/kg of intravenous fentanyl was given in cases where the FLACC score was 3 or above. HR and MAP were monitored at the time of PACU admission, again at 5 and 10 minutes, and then every 10 minutes until the discharge criteria were fulfilled. Any postoperative complications, such as bradycardia, hypotension (defined as a decrease of less than 20% from baseline values), or hypersensitivity reactions, were duly documented. As part of the study's outcome measures, the incidence of postoperative vomiting was also reported. Patients were observed in the PACU until they met all discharge criteria, which included full alertness, calm demeanor, stable hemodynamics, a PAED score of less than 10, and oxygen saturation levels exceeding 92% on room air. The primary outcome of the study was the incidence of postoperative emergence delirium, as assessed by the PAED scale upon admission to the PACU. Secondary outcomes comprised intraoperative vital signs, the incidence of intraoperative complications, PAED scores following extubation, the cumulative dose of rescue sedation with propofol in the PACU, FLACC scores, the total dose of rescue analgesia required, postoperative hemodynamic stability, and the overall incidence of postoperative nausea and vomiting (PONV).

Sample size calculation

G*Power 3.1.9.2 (Universität Kiel, Germany) was employed to calculate the sample size based on the primary outcome measure, namely emergence delirium (ED). The ED was anticipated to occur in the DEX group and the ketamine-propofol group, with PAED scores of 1.55 ± 2.195 and 4.70 ± 3.988, respectively, as documented in the prospective randomized study by Amer and Abdallah [12]. To achieve a statistical power ($1–\beta$) of 90% and to maintain a type I error rate (α) of 0.05, the initial calculation determined that a total of 46 patients (23 per group) would be necessary. An additional six patients were incorporated to account for potential dropouts, resulting in a final sample size of 52 patients, with 26 patients assigned to each group.

Statistical analysis

SPSS v26 (IBM Inc., Chicago, IL, USA) was employed to conduct statistical analysis. An unpaired Student's t-test was used to compare groups, and continuous variables were given as means with standard deviations. Whereas, depending on the situation, analyses were carried out using either Fisher's exact test or the chi-square test, with frequencies and percentages being used to represent categorical variables. A two-tailed P value below 0.05 was used to assess statistical significance.

Results

A total of 58 patients were evaluated for eligibility in this study. Five patients were excluded based on the criteria, and one patient chose not to participate. The remaining patients were randomly split into two groups of 26 each. The statistical analysis encompassed all enrolled patients who were subsequently followed up (Figure 1). There was no substantial difference between the two groups with respect to basic clinical and demographic characteristics, duration of surgery, and incidence of intraoperative bradycardia and hypotension (Table 1). HR, MAP, and SpO_2 were measured at time points, starting on admission, then every five minutes until the end of surgery, and then after extubation, where there was no considerable difference between groups at

any time point (Figure 2). Postoperative PAED and FLACC scores were insignificantly different between the two groups. Postoperative rescue analgesia was more experienced among Group D than Group K patients; moreover, postoperative rescue sedation was more experienced by Group K than Group D patients, but without a significant difference between groups regarding either rescue analgesia or sedation (Table 2). HR, MAP, and SpO_2 were measured during PACU stays, starting on admission, after 5, 10, 20, and 30 minutes, with comparable outcomes exhibited between the groups (Figure 2).

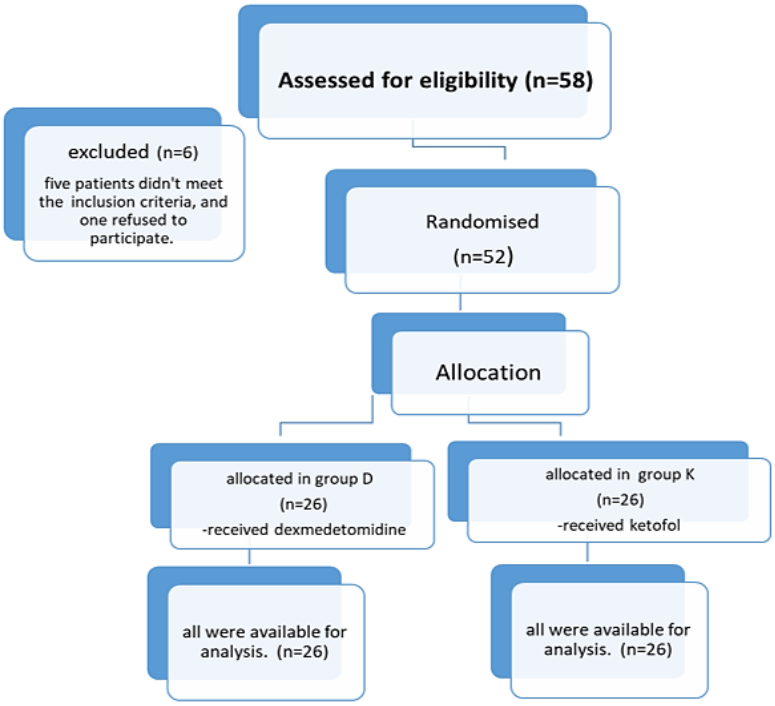

Figure 1- CONSORT chart of patients.

Table 1- Basic demographic characteristics, duration of surgery, and incidence of intraoperative bradycardia and hypotension of patients.

		Group D (n=26)	Group K (n=26)	P
Age (Years)		4.6±0.67	4.7±0.77	0.459 [b]
Sex	Male	14 (53.8%)	11 (42.3%)	0.419 [a]
	Female	12 (46.2%)	15 (57.7%)	
ASA physical status	I	24 (92.3%)	23 (88.5%)	1.00 [c]
	II	2 (7.7%)	3 (11.5%)	
Duration of surgery (mins)		114.8±5.1	115.1±3.2	0.889 [b]
Bradycardia		10 (38.5%)	6 (23.1%)	0.229 [a]
Hypotension		2 (7.7%)	3 (11.5%)	1.00 [b]

Data are presented as mean ± SD or frequency (%); a: Chi-square test; b: Independent samples T-test; c: Fisher's exact test; ASA: American Society of Anesthesiologists; group D: Dexmedetomidine; group K: Ketofol.

Table 2- Postoperative PAED and FLACC scores and postoperative rescue analgesia and sedation among patients.

		Group D (n=26)	Group K (n=26)	P
PAED score	On admission	9.1±1.4	9.9±1.1	0.125
	After 5 minutes from admission to PACU	8.23±0.8	8.54±0.7	0.166
	After 10 minutes from admission to PACU	8.3±1.15	8.7±0.74	0.122
	After 15 minutes from admission to PACU	7.73±0.9	8.15±0.78	0.08
	After 20 minutes from admission to PACU	6.8±1.2	7.2±0.99	0.211
	After 25 minutes from admission to PACU	6.2±0.99	6.7±1.3	0.1
	After 30 minutes from admission to PACU	6.04±1.04	6.57±1.2	0.096
FLACC score		2.78±1.4	1.95±1.14	0.137
Rescue analgesia		8 (30.8%)	6 (23.1%)	0.532

Rescue sedation	5 (19.2%)	7 (26.9%)	0.510

Data are presented as mean ± SD and analyzed using an independent sample T-test; Group D: Dexmedetomidine; Group K: Ketofol; PAED: post-anesthesia emergence delirium; PACU: post-anesthesia care unit; FLACC: Face, Legs, Activity, Cry, and Consolability.

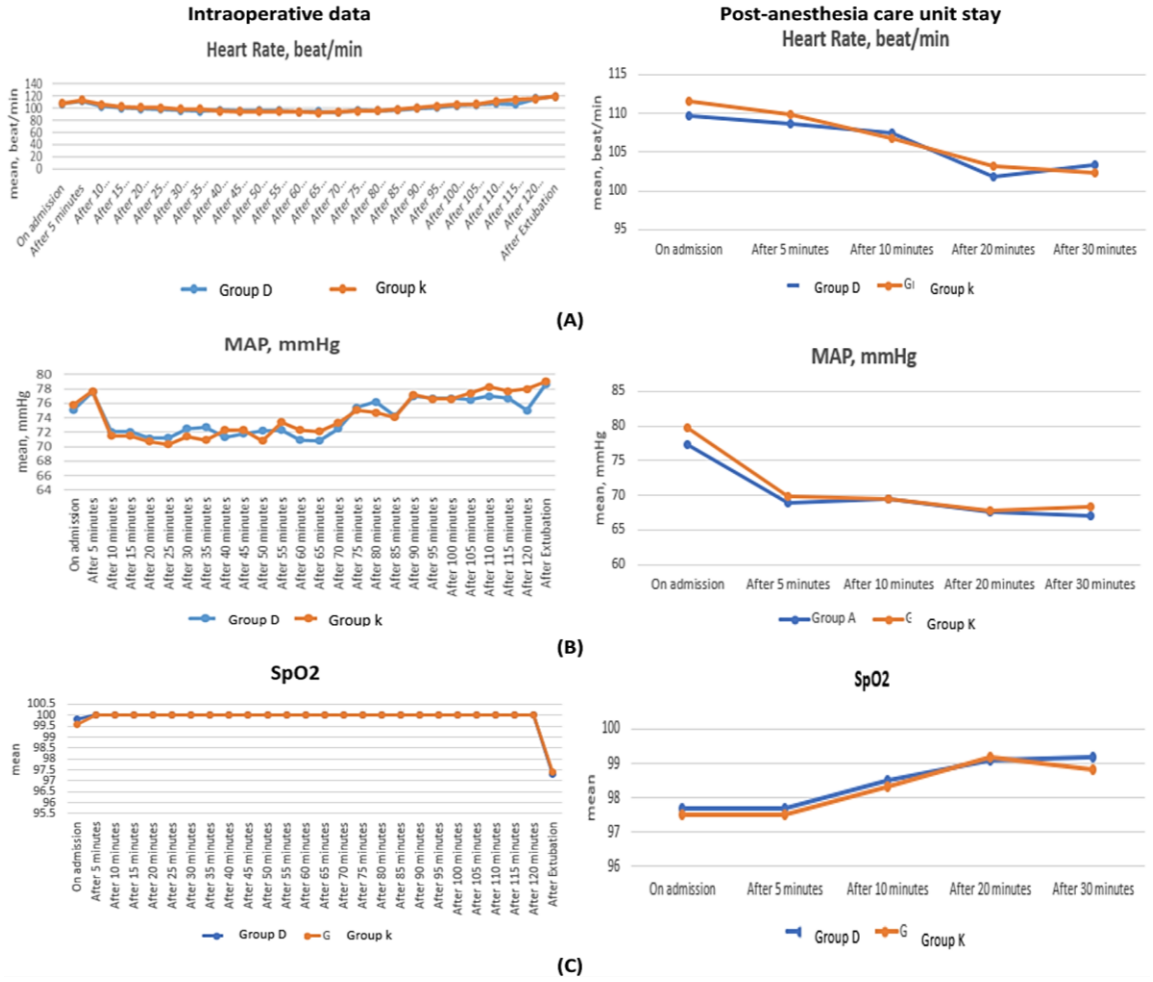

Figure 2- Line graph showing (A) heart rate, (B) mean arterial pressure, and (C) oxygen saturation.

Discussion

Few studies have examined the efficacy of Ketofol and DEX in preventing ED in children, as far as we are aware. In the present investigation, regarding PAED scores during PACU stay, the DEX group had lower scores than the ketofol group patients without a statistically significant difference between them at any time point. Moreover, postoperative rescue sedation was more experienced by the ketofol group than the DEX group patients, without a statistically significant difference between groups.

In agreement with our results, Jayaraj et al. [13], Prasad and colleagues [11], and Ali and collaborators [10] exhibited that the PAED scale score was insignificantly different between both the DEX group and ketofol group at any time point. In our study, regarding intraoperative and during PACU stay, HR, MAP, and SPO2 were insignificantly different between the two groups at any time point. Similar to our observations, Jayaraj and colleagues [13] observed no substantial differences in HR, MAP, and oxygen saturation between the two groups throughout the surgery until extubation. But compared to DEX, the ketofol group had substantially higher HR and MAP after extubation and 10 minutes later. This difference may be due to variations in procedures, timing of administration, and anesthetic doses. In contrast to the DEX group, which received 0.3 µg/kg DEX, we gave 0.2 µg/kg/h of DEX and 0.6 ml/kg/h of Ketofol. In the Ketofol group, they utilized 0.25 mg/kg of ketamine and 1 mg/kg of propofol. Also, Prasad et al. [11] reported that intraoperatively and during the period in the PACU, hemodynamics was insignificantly different between both the DEX and the ketofol groups. Moreover, Ali et al. [10] discovered that the groups given Ketofol and the

DEX had much higher HR and MAP 10 minutes after extubation.

In the current study, patients in the DEX group were more likely to have bradycardia, nausea, and vomiting during surgery than those in the Ketofol group; however, there was no statistically significant difference between the two groups when it came to intraoperative hypotension. Similarly, Hussien and collaborators [14] reported that postoperative bradycardia was significantly more experienced among the DEX group than Ketofol group patients. This significant difference may be related to the different surgeries and sample sizes also; they excluded children with ASA II, while we included them. Although the rates of vomiting were comparable in the DEX and propofol groups, the prospective randomized research by Amer and Abdallah [12] found that the DEX group had a much increased frequency of hypotension.

In our study, 30.8% of group A experienced postoperative pain compared to 23.1% in the other group, without a significant difference between them. In line with our results, Jayaraj and colleagues [13] and Prasad and collaborators [11] stated that the pain score was insignificantly different between the dexmedetomidine group and the Ketofol group. Comparable with our findings, Biricik et al. [15] discovered that reducing the occurrence of ED and the requirement for analgesics in children is possible by mixing ketamine with propofol during sevoflurane anesthetic induction. In our study, the emergence time was longer among ketofol group than the DEX group patients, without a statistically significant difference between them. In consistency with our finding, Prasad et al. [11] found that emergence time was insignificantly different between both DEX and Ketofol groups. Other studies that may support our findings: Alassaf et al. [16] demonstrated that DEX significantly reduced ED incidence and lowered the requirement for rescue analgesia in the pediatric population following ophthalmic surgeries compared to placebo or other medications. Furthermore, Abdelzaam and Mahdy [17] demonstrated that compared to normal saline, ketamine plus DEX substantially decreased the occurrence and severity of ED. Limitations of this study included that the sample size was relatively small. Each of which may shed light on the direction of future research. The results may differ from those seen in other studies because this one only involved one location.

Conclusion

Ketofol demonstrates comparable efficacy to DEX for the prevention of ED in the pediatric population undergoing squint surgeries with stable hemodynamics.

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